Chapter 11
How Does Modularity in the Genotype–Phenotype Map Shape Development and Evolution?

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Abstract Traits do not evolve independently, as genetic and developmental associations affect the variation that is expressed in populations and that is available for evolutionary change. In this chapter, we explore the causes and consequences of structured variation, introducing the concept of modularity, exploring some possible causes for modular organization in different levels, and, finally, discussing how the introduction of new variation can evolve.

11.1 Evolution and Variation

> Hence if man goes on selecting, and thus augmenting, any peculiarity, he will almost certainly modify unintentionally other parts of the structure, owing to the mysterious laws of correlation. Darwin (1872)

Evolution proceeds by many different processes, all of which depend on the variation present in natural populations. The probability of fixation or loss of a neutral variant due to drift depends on its frequency in a population. The increase or decrease via natural selection of the frequency of an allele that has an effect on fitness depends on the standing variation in that locus. Therefore, the fate of a new variant depends on the population in which the new variant appears, whether it is neutral or not. Advantageous variants that are quite frequent may be lost in small populations, while even the smallest advantage in fitness can guarantee that a rare variant will be fixed in very large populations. In an analogous way, the change in the distribution of a phenotype in a population depends on its standing variation, and the details of this variation can profoundly alter the evolutionary process. For example, consider a hypothetical selection regime that operates as to increase the length of the left arm of the individuals in a population. Individuals that have a long left arm leave more

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J. M. Martín-Durán, B. C. Vellutini (eds.), *Old Questions and Young Approaches to Animal Evolution*, Fascinating Life Sciences,
https://doi.org/10.1007/978-3-030-18202-1_11

offspring, and if the trait is heritable, the offspring of these individuals have themselves longer left arms. So, the mean length of the left arm increases due to natural selection, but the right arm is seldom very different from the left arm, and so these long left-armed individuals also have long right arms, and the mean of the right arm also changes between generations, due to a process we now recognize as correlated response to selection (Lande and Arnold 1983). This indirect correlated response happens because left and right arms are genetically correlated, and when the genes for long left arm are passed on to the next generation in large numbers, they are also genes for long right arm, resulting in an evolutionary change in a structure that was not under selection. This example illustrates that, while individuals are composed of multiple parts, these parts are not independent, and how they are related in a population can indeed alter evolutionary outcomes. This is a problem familiar to all animal breeders throughout history (Hazel 1943), as attempts to selectively breed individuals in order to improve some aspect of the populations invariably leads to changes to other aspects. This problem suggests that a more complete understanding of diversification and evolution must somehow include a model for the evolution of the relations between traits.

Phenotypes are always a complicated affair. Even the simplest of biological structures is composed of several different parts and must be created from scratch in each individual, requiring several thousand proteins and molecules to interact in some way. All the different traits in an individual must be formed through development, and the blueprints for this process are encoded in the genome. So, if a phenotype is formed by development, then it must follow that all the variation in these phenotypes in a population must also be created, or at least mediated, by development. There are several sources of variation in biological populations. Some proportion of the variation in a population will be due to differences in the genetic makeup of individuals, while some other part will be due to variation inherent to the development process, some part will be due to environmental differences between individuals, and so on. Because all these sources of variation must be channeled through development, the structure of development imposes constraints in the variation that is ultimately expressed in a population. If the left and right arm share, to some degree, some developmental pathways, variation in these pathways will lead to correlated variation in both arms. The path between genetic variation and phenotypic variation is crucial and can be expressed in the genetic architecture.

11.2 Genetic Architecture and the Genotype–Phenotype Map

Genetic architecture is the structure of the relation between genotype and phenotype (Hansen 2006). Genetic variation acts through some sort of developmental process to produce variation in the phenotype. But not all genetic variation will affect the full phenotype of the individual. Some parts of the genome only affect very specific

phenotypes, while others will have generalized effects in the whole organism. Genetic architecture defines this relation and can have important consequences to the evolutionary process, while at the same time being modified by it.

One way of understanding genetic architecture is by constructing genotype–phenotype maps (GP maps), which are mappings between genetic sequences and phenotypes. Here, phenotypes can refer to a broad range of traits, from exceedingly simple to the mind-bogglingly complex. Perhaps the simplest possible example of a GP map that is still relevant in biology is the secondary structure of an RNA molecule. For a given RNA molecule sequence (genotype), the very simple development of folding the molecule results in a particular shape (phenotype) (Ancel and Fontana 2000). This shape is uniquely determined by the sequence, but different parts of the sequence interact in complicated ways to generate the full final shape. Because of the richness of the relation between sequence and shape, this simple system has been extensively used as a model of evolution (Stadler and Stadler 2006) and indeed presents several properties that we aim to understand in more complex phenotypes, such as modularity and robustness. We can also think of the genetic architecture and GP map of more complex traits, such as behavior, gene expression, skeletal structures, growth, body shape, body composition, and so on. Evolution of these complex traits, composed of several interacting parts, is profoundly influenced by genetic architecture.

We often rely on mathematical models to explore the consequences of assumptions on the structure of the GP map. One of the earliest models of complex phenotypic change, Fisher's geometric model (Fisher 1930), already presented formidable consequences to evolution (Orr 2000). In this model, Fisher assumed a completely pleiotropic genetic architecture. Pleiotropy is the situation where one gene affects more than one unrelated trait, and in Fisher's model, all genes affected all traits. An individual is represented as a point in some high-dimensional continuous phenotype space, with each dimension representing some trait in the individual, and fitness is given by a selective surface with a single optimum. Mutation is represented by a shift in all traits, and this can be interpreted as a vector sum between the initial position and a small random vector representing mutation. This mode of mutation implies complete pleiotropy, as every mutation can potentially affect every trait. Furthermore, this geometric interpretation of mutation gives the model its name. If the individual is not at the phenotypic optimum, a mutation might increase or decrease fitness. If the mutation increases fitness, it can be fixed via natural selection and lead to adaptation, with probability proportional to the increase in fitness. Under this model, Kimura (1983), and later Orr (2000), showed that the rate of adaptation decreases with the number of traits, an effect called "cost of complexity," as more complex organisms would be slower to adapt. This cost appears because, under complete pleiotropy, only a small proportion of random mutations would alter all the traits of an organism in a beneficial way, and most mutations will move the individual away from the optimum. This result was shown to be fairly robust to some possible mitigating assumptions regarding the genetic architecture (Welch et al. 2003) and so posed a difficult mismatch between observation and theory, as complex organisms composed of many traits exist and seem to have no

problem adapting to many environments, sometimes with remarkable speed (Kinnison and Hendry 2001).

This paradox only became tractable in light of explicit tests of the assumptions of the geometric model, namely, the pattern of pleiotropy in the GP map and its consequences to mutation. In the last few decades, we have begun to experimentally explore the genetic architecture of complex traits using molecular mapping techniques, which allows us to relate genetic variation to phenotypic variation (Mackay 2001). Quantitative trait locus (QTL) studies and genome-wide association studies (GWAS) have allowed us to investigate which variants are related to disease, to improve our agricultural efficiency, to develop optimal breeding strategies, and to further our understanding of the evolutionary process by directly assessing genetic architecture. Using QTL mapping, Wagner and collaborators (Wagner et al. 2008) investigated the assumptions the geometric model made with regard to the GP map and showed that the assumptions of the geometric model are not reasonable. This incongruence between data and Fisher's early model of genetic architecture can be summarized by two key points. First, pleiotropy is not global, and the vast majority of loci affect only a small number of traits. Second, the pleiotropic effect of loci onto a trait does not decrease with the loci's level of pleiotropy. In other words, there is a nontrivial scaling of genetic effects with the degree of pleiotropy. It turns out these details matter a great deal here, and these properties of the genetic architecture of complex traits we were only recently able to quantify experimentally are, therefore, fundamental for the evolvability of complex organisms (Wagner and Zhang 2011). We may ask how these evolvable genetic architectures came to be.

11.3 Traits and Modules

> It [adaptation of traits] can only be workable if both the selection between character states and reproductive fitness have two characteristics: continuity and quasi-independence. Continuity means that small changes in a characteristic must result in only small changes in ecological relations; a very slight change in fin shape cannot cause a dramatic change in sexual recognition or make the organism suddenly attractive to new predators. Quasi-independence means that there is a great variety of alternative paths by which a given characteristic may change, so that some of them will allow selection to act on the characteristic without altering other characteristics of the organism in a countervailing fashion; pleiotropic and allometric relations must be changeable. Continuity and quasi-independence are the most fundamental characteristics of the evolutionary process. Without them organisms as we know them could not exist because adaptive evolution would have been impossible. Lewontin (1979)

> But what are the structural features that make stepwise improvement possible? The key feature is that, on average, further improvements in one part of the system must not compromise past achievements. . . . Wagner and Altenberg (1996)

The very existence of (*semi*)individualized traits depends on one ubiquitous aspect of evolved genetic architecture and genotype–phenotype maps: modularity. Modularity can be defined very generally as a property of a system whose parts are

assembled into groups which are tightly associated while maintaining a relative independence between groups. In the context of biological organisms, modularity appears at several levels of organization. Traits are, in a sense, modules, recognizable units with relative independence, and indeed Richard Lewontin went so far as to postulate that this subdivision is fundamental to adaptation (Lewontin 1979). The cost of complexity paradox illustrates this nicely: without a genetic architecture that provides some level of independence between traits, adaptation cannot occur. It is not surprising then that these identifiable units we recognize as traits are modified during evolution without severely affecting the rest of the organism, and, accordingly, their independence is reflected in their genetic architecture. Hansen (2003) points out that a modular genetic architecture is not the only way to achieve independent traits, but the observed modular organization at several levels of organization, from gene expression to morphology, suggests a deep underlying principle of organisms (Wagner et al. 2007).

Modularity occurs at several levels, and traits are organized into larger modules, which may, for example, perform a given function or form a structure. Olson and Miller (1958) founded a research project based on the holistic investigation of organisms and their organization into interconnected groups and in their interrelations from the whole individual. Their seminal book championed the idea of morphological integration, which captures the varying degrees of interdependence traits must poses in order to come together into functional units that can then perform the functions that are required of them. Olson and Miller pointed out that we can identify these groups of traits by their correlations, as traits in a functional module should covary together, as a consequence of their mutual requirements for the performance of a function. The importance of these modules to evolution was elegantly posited by Wagner and Altenberg (1996), who brought the idea of a modular architecture as a central concept of biological organization. These modules of correlated morphological traits could then change with relative independence during evolution, while the genetic correlations within modules facilitate a coordinated response to selection, maintaining their function if one of the elements within a module were to be altered (Cheverud 1982, 1984).

The advent of QTL mapping also allowed us to investigate how the relative independence between these sets of traits related to the genetic architecture. Studies in several levels of biological organization show that the genetic architecture underlying these modules is also modular, as the pleiotropic effects of genes are more often restricted to traits within these groups. This is true of gene expression (Hartwell et al. 1999; Segal et al. 2003) all the way up to morphological traits (Mezey et al. 2000). Modularity is also expressed in development, as the several processes involved in the formation of a given trait will also be relatively separate from one another and conceptually different. To see this, we may return to the example of the left and right arm. Both develop separately, and so in some sense, each is formed by a separate developmental module, but both share a great deal of genetic information and tend to evolve and so are the same evolutionary module. However, these relations are not static, as evolutionary and developmental modules can be created or collapsed during evolution. One familiar example of this kind of modular

reorganization is the case of the association between upper and lower limbs in humans, which became less associated as a result of changes in our mode of locomotion (Young et al. 2010). Changes in the pattern of correlations between phenotypic traits suggest the underlying modular GP map responsible for the genetic associations we observe in populations can be altered by evolution. This realization has important consequences, as we establish a feedback between selection and associations. We now turn to the first part of this feedback.

11.4 Evolution of Modular GP Maps

Advances in QTL mapping have allowed us to probe the genetic architecture and describe the mechanistic basis for the evolution of genetic architecture and the origin of the genetic variation that can allow changes in the GP map. Cheverud and colleges have shown that gene interactions are major sources of variation in pleiotropic patterns (Wolf et al. 2005; Pavlicev et al. 2008). Epistasis, gene effects due to the interaction between different loci, greatly enhances the variational possibilities in natural populations by changing which loci affects which traits. More importantly for our discussion, variation in pleiotropic relations provide the necessary ingredient for us to understand the evolution of modularity (Wagner and Altenberg 1996). The link between function and modules of phenotypic traits suggests that modular organization is an adaptation, and so we focus on selective explanations for the modular organization of genetic architecture. On the other hand, plausible neutral mechanisms for the emergence of modularity in some organizational levels have been proposed in the literature (Wagner et al. 2007; Lynch 2007). Furthermore, since modularity is so general and occurs at different levels of biological organization, it is hard to imagine this property evolved by a single mechanism at all scales, and therefore each kind of association might require different explanations. Perhaps the ubiquity of modularity reflects these different roads that lead to it. Therefore, how modularity evolves remains an open question, and because all of these modular architectures at different levels are already established in nature, the work on the possible causes for its evolution relies heavily in mathematical and computational models.

One of the important problems I have emphasized that is solved by modularity is the need for robustness, in the sense that changes in one part of the organism do not interfere with others. Ancel and Fontana (2000) used a model for the secondary structure of RNA molecules to study the origins of modularity, defined as the independence between different parts of the RNA molecule in the process of melting under increasing temperature. In a modular molecule sequence, secondary structure is lost in the different parts of the molecule (modules) independently, while in a non-modular sequence, the whole molecule continually changes its configuration during melting. In their simulations, stabilizing selection was applied to a population of evolving sequences, based on their secondary structures. This selection for robustness had a number of consequences in the GP map of the sequences. Selected

sequences were more robust to mutations and showed less phenotypic variation at intermediary temperatures, there was a convergence of phenotypic and genetic variation, and the selected sequences also became more modular (i.e., conformations in different parts of the molecule become more independent). This suggests that direct selection for robustness can lead to the evolution of modularity, but the increase in evolvability due to modularity is not present in this simplified system, so the analogy breaks down somewhat. In any event, it is quite possible that selection for robustness is a driver of the evolution of modularity.

Selection for evolvability has also been proposed as a possible cause of modularity. In quantitative genetics, evolvability is defined as the available variation for the response to selection, and Pavlicev et al. (2011) proposed a model based on the existence of genetic variation for the association between two traits. This variation was expressed in the form of an additive Mendelian polymorphism for the correlation between two traits in a population. Homozygous individuals for one allele show high correlation between the two traits, while homozygotes for the other allele show no correlation, and the heterozygotes show intermediary correlations. Selection was modeled deterministically using the response to selection equation from quantitative genetics theory (Lande 1979). Under this model, selection for coordinated evolution of the two traits (simultaneous increase or decrease in the value of the traits) leads to the fixation of the allele encoding high correlation, and corridor selection, when one trait is held constant and the other traits are selected for increase, leads to the fixation of the allele encoding low correlation. In these two scenarios, the allele that provides the highest amount of variation in the direction of selection is fixed, and so selection increases evolvability by either integrating or separating trait variation. We observed a similar effect of directional selection in a fully mechanistic model, in which pleiotropy and gene effects were allowed to change via mutation in a large population of simulated individuals. Using this model, we were able to show in Melo and Marroig (2015) that stabilizing selection and drift are not viable candidates for the emergence of modularity in complex phenotypes composed of many traits. Stabilizing selection was theoretically a possible driver of modularity (Lande 1980; Cheverud 1984) and has been shown to be effective in a small number of traits (Jones et al. 2007, 2014), but the structure of high-dimensional variation prevents stabilizing selection from being efficient for multiple traits. This difficulty appears because stabilizing selection is very efficient at increasing within-module correlations, but not efficient at reducing between-module correlations, so modules can't form. We looked at the effect of directional selection in the covariance structure and the pattern of pleiotropic relations (Melo and Marroig 2016), we see that directional selection is a powerful driver of modularity, and traits that are selected in the same direction in the simulations rapidly become more associated than traits that are selected in different directions. Also, we show that corridor selection can create complex patterns of correlations, as traits under directional selection become more associated within themselves, while traits under stabilizing selection maintain an intermediate level of correlation, and the correlation between these two groups is reduced. In all simulation, the changes in the correlation structure are due to selective

changes in the GP map, in which pleiotropic relations are altered by selection, increasing evolvability.

Moving to some non-morphological traits, selection for more than one function has also been shown to promote modularity in gene regulation networks, while single objective networks were more integrated (Espinosa-Soto and Wagner 2010). This is somewhat analogous to the continuous traits case we discussed above, where different parts of the system become adapted to one function. These modular regulation networks are also more stable and robust. Interestingly, when working with neural networks, selection for multiple objectives was not sufficient for creating modules in work done by Clune et al. (2012). In their simulations, in addition to the selection for multiple outputs, the neural networks only became modular with the addition of a cost for connections between nodes of the neural network. While only suggestive, this provides a possible explanation to why modularity and not other pleiotropic organization that provide evolvability (see Pavlicev and Hansen 2011 for examples) are more common in nature: there could be a cost to maintaining high levels of pleiotropy, even if not in the form of low evolvability.

All the models we have seen so far treat development as a black box that does not influence modularity, which is clearly a rather strong simplification. In an attempt to include the complications of development, Watson et al. (2014) use an ingenious strong selection weak mutation model that allow them to include explicit developmental interactions to the GP map. In this model, both the initial (embryonic) traits and the interactions between these traits in all phases of development are under genetic control. At each step of development, new interactions add complexity to the final adult phenotype, and this adult phenotype is exposed to selection regimes that can change every few thousands of generations. Traits in this model tend to become more associated throughout development when they are selected in the same direction in all selection regimes and become independent when they are selected in different directions. Also, selection for different independent modules can lead to developmental interactions that allow composition of these modules to form novel morphologies that were not the initial selected states, an emergent form of complex organization. We now turn to these emergent properties of modularity that can profoundly facilitate adaptation.

11.5 Modular Variability

> Evolvability is the genome's ability to produce adaptive variants when acted upon by the genetic system. This is not to say that the variants need to be 'directed' (Foster and Cairns 1992) for there to be evolvability, but rather, that they cannot be entirely 'misdirected,' that there must be some small chance of a variant being adaptive. The situation is analogous to obtaining a verse of Shakespeare from monkeys banging away on typewriters. Typewriters make this far more likely than if the monkeys had pencil and paper. The type-writers at least constrain them to produce strings of letters. Similarly, the genotype-phenotype map constrains the directions of phenotypic change resulting from genetic variation. Wagner and Altenberg (1996)

Perhaps the most interesting consequence of the modular structure of the GP map and development is the effect this organization has on variability. Günter Wagner has often drawn the distinction between variation and variability (Wagner and Altenberg 1996). For our purposes, *variation* refers to the expressed differences between individuals in a given population: how different are they, or how differences between individuals are correlated. Using variation we might predict how a population evolves under drift of natural selection or make inferences regarding variational modules. *Variability*, on the other hand, refers to the ability of the population to generate variation. Wagner likens variability of an organism to the solubility of a substance. Solubility does not refer to the physical state of being in solution but instead to a property that a given substance has that defines how it behaves when in solution. Likewise, a population of genetically identical individuals has no genetic variation, but still has variability, defined by its mutational properties. (For example, new mutations could have correlated effects on many traits due to shared development and genetic architecture.) Variation present in populations that is available for selection must ultimately come from mutation. We are often told that mutation is random, but this is a rather strong simplification. In what sense are mutations random? Dan Graur (2015, p. 34) points out that mutations are not random with respect to genome position or mutation type and that mutational effect on fitness are species specific, gender specific, developmental stage specific, and several other nonrandom conditions. The only way in which mutations are random is in that the probability of a given mutation is the same regardless of whether it is advantageous, neutral, or deleterious in the individual in which it appears (Luria and Delbrück 1943). The key point is that new mutation can be structured by variability, and so new variation can also be structured. In quantitative traits, we can describe and quantify variability by using the mutational matrix, the covariance matrix of mutational effects. This can be done experimentally using mutation accumulation lines, measuring the correlation between phenotypic changes that appear in these lines due to mutation. We expect that, under some general conditions and given enough time, the genetic variation in a population come to mirror the mutational matrix (Lande 1980; Cheverud 1984; Jones et al. 2007). The form of the mutational matrix, and of variability in general, depends on the GP map and on development, as traits that share pleiotropic genes or developmental pathways will be jointly altered by mutations. So, all the results we have seen on selection altering GP maps have consequences to variability and to the introduction of new variation in natural populations.

Models for the evolution of the mutational matrix in quantitative traits reveal the possibility for interesting dynamics. Jones et al. (2014) used an individual-based model with epistatic interaction to study the evolution of the mutational matrix. Epistasis is important because it opens the door for complex interactions and can lead to variation in mutational correlations. Under their model, the mutational matrix of two quantitative traits evolves to match the selection surface matrix, and so new mutations are biased by past selection. Consequently, variation that is introduced by mutation tends to respect the past selective surface, and if this surface is stable, new mutations have a lower probability of being deleterious. This kind of reorganization of variability also appears under directional selection in the model from Pavlicev and

Hansen (2011) and in Draghi and Wagner (2008), which uses a different scheme for the evolution of pleiotropic relations and trait associations.

While these mathematical and computational results are remarkable, they are difficult to explore experimentally. Epistasis and allele interactions have been shown to contribute significantly to the phenotypic covariation in complex traits (Cheverud et al. 2004; Wolf et al. 2005, 2006; Pavlicev et al. 2008; Huang et al. 2012), but we still lack a deep understanding on how this variation is explored by natural selection and evolution. However, recently studies in natural populations and artificial selection have begun to uncover the effects of selection on covariation. Working with morphological skull traits, Assis et al. (2016) (in natural populations) and Penna et al. (2017) (in artificial selection experiments) have shown that variation can indeed be reorganized in the direction of selection, increasing potential future evolvability, the same kind of effect observed in simulations in Pavlicev et al. (2011) and Melo and Marroig (2015). Conversely, several studies have documented the opposite effect, in which directional selection acts in a more traditional manner in multivariate traits, eroding the genetic variance in the direction of selection (Walsh and Blows 2009). Careau et al. (2015) carefully documented this effect in behavioral traits in mice using a large selection experiment, in which response to selection plateaued after several generations of selection. These differences might be explained by differences in the genetic architecture of these two different types of traits, but more detailed studies are certainly needed.

11.6 Phenotypic Space and Concluding Remarks

This remarkable feedback between selection, variation, and variability suggests a deeper consequence of the structure of the GP map and phenotypes. Most of our understanding and descriptions of phenotypes assume that the space in which phenotypes exist is continuous, Euclidean, and that we can measure how close two phenotypes are using a natural distance measure. In this framework, we rely on carefully chosen adaptive landscapes to explain why some portion of the phenotypic space are not explored and to account for the emergence of modularity. If not for selection, this framework implicitly places no limitations on the possible phenotypes of organisms. Stadler et al. (2001) provide a different perspective, wherein phenotypic space is such that simple Euclidean distances do not make sense (like the surface of Earth at large scales), and phenotypes are not restricted only by selection but also by development and genetic architecture. In this space, distances depend on genetic proximity and the GP map, thus limiting the set of paths that the mean phenotype of a population can take. In this view, modularity and robustness and several other unexplained complexities in phenotypic evolution are a reflection of the underlying metric imposed by the GP map. A simpler and less encompassing version of this idea was already present in the quantitative genetics literature. For example, Lande (1979) explicitly stated that a population's distance to an adaptive peaks should be measured in genetic variance distance, not morphological distance,

and see Steppan et al. (2002) and Melo et al. (2016) for an exploration of the macroevolutionary consequences of this fact.

Glossary

Complex phenotype Multivariate phenotypes, composed by several interacting traits and controlled by several loci. Gene expression, body composition, and skeletal structures are examples of complex phenotypes.

Epistasis Changes in phenotype caused by interactions between two of more loci.

Genetic architecture The structure of the relation between genotype and phenotype. Which regions of the genome affect which phenotypes.

Genetic effects How a particular allele is expected to change the phenotype of an individual in relation to the population mean. This can depend on the population allele frequencies, other alleles, or the environment.

Genotype–phenotype map The mapping between a genetic and phenotypic variants.

Modularity A pattern of association between parts where some groups of elements are strongly interrelated among themselves, and elements belonging to different groups are weakly interrelated.

Pleiotropy The phenomenon in which an allele affects multiple distinct traits.

Variation and variability Variation refers to the realized differences between individuals in a population, while variability is the ability to generate this variation.

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